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Add-on montelukast vs double-dose budesonide in nonasthmatic eosinophilic bronchitis: A pilot study

Chuang Cai [a,b,*,d], Mu-zhi He [c,d], Shu-qing Zhong [b,d], Yan Tang [b,d], Bao-qing Sun [b,d], Qiao-li Chen [b,d], Nan-shan Zhong [b,d]

[a] Department of Respiratory Medicine, Hangzhou Red Cross Hospital, HuanCheng Dong Rd. 208, Hangzhou 310003, China
[b] Guangzhou Institute of Respiratory Disease, Rd. Yanjiang 151, Guangzhou 510120, China
[c] Department of Geriatrics, Guangzhou General Hospital of Guangzhou Military Command, Rd. Liuhua 111, 510010, China

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KEYWORDS
Montelukast;
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Cough visual analogue scale

Summary
Background: Budesonide at 800 μg/d is generally suggested for treatment of nonasthmatic eosinophilic bronchitis (NAEB). In asthma, adjunctive therapy with montelukast has been shown to confer addictive anti-inflammatory effects to inhaled corticosteroid (ICS). However, whether such effects could be extrapolated to NAEB is not known.
Objectives: To study the efficacy and tolerability of add-on therapy with montelukast as compared to double-dose ICS in suppressing airway eosinophilia and decreasing cough severity in NAEB.
Methods: In a randomized controlled trial, 26 nonsmoking, steroid-naïve NAEB patients presenting with chronic cough were treated with 800 μg/d budesonide or 400 μg/d budesonide plus montelukast 10 mg/d for 4 weeks. Cough visual analogue scale (CVAS) and eosinophil differential ratio in induced sputum (Eos) were monitored at baseline, Week 1, 2 and 4. Adverse events during treatment were recorded.
Results: The two groups were comparable in age, gender distribution, cough duration, FEV_1% predicted, FEV_1/FEV ratio, baseline CVAS and geometric mean of Eos. Both regimens significantly reduced Eos and CVAS throughout the treatment course, with abrogation of sputum eosinophilia at end of therapy. There was no significant difference between the two groups in reduction of Eos and CVAS at all time points. Both regimens were well tolerated.

Abbreviations: ACCP, American College of Chest Physicians; AR, allergic rhinitis; BPT, bronchial provocation test; BUD, budesonide turbuhaler; BUD-MONT, montelukast and budesonide combination therapy; CVA, cough-variant asthma; CVAS, cough visual analogue scale; cysLTs, cysteinyl leukotrienes; Eos, eosinophil differential count in induced sputum; GERD, gastroesophageal reflux disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GM, geometric mean; ICS, inhaled corticosteroids; LFT, lung function test; LTRA, leukotriene receptor antagonist; MONT, montelukast; NAEB, nonasthmatic eosinophilic bronchitis; PC_{20}, provocative concentration of histamine causing a 20% reduction of FEV_1.

* Corresponding author. Department of Respiratory Medicine, Hangzhou Red Cross Hospital, HuanCheng Dong Rd. 208, Hangzhou 310003, China. Tel.: +86 571 56109772; fax: +86 571 85186042.
E-mail address: skinblack1966@yahoo.com.cn (C. Cai).
[d] All the authors contributed equally for the study and should be listed as co-first authors.

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Conclusions: This preliminary study demonstrated that add-on montelukast might be an effective and well tolerated alternative to the generally suggested dose of ICS in treating steroid-naive NAEB, with suppression of eosinophilic inflammation, reduction of cough severity and sparing of ICS doses. (NCT01121016).

Introduction

Defined as airway eosinophilia without evidence of airway hyperresponsiveness and variable airflow obstruction, nonasthmatic eosinophilic bronchitis (NAEB) is one of the most common causes of chronic cough, accounting for 10%–30% of patients seen in respiratory specialist clinic.[1,2] At present, inhaled corticosteroids (ICS) is the first-line pharmacotherapy recommended by the 2006 American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines on chronic cough due to NAEB.[1] Although the variety of ICS, its optimal dose and course has not been defined by the guidelines,[1] inhaled budesonide (BUD) at 800 μg/d or the equivalent dose of fluticasone is generally suggested[3] and used to treat NAEB.[2,4,5] Occasionally, oral corticosteroids are required when eosionophilic inflammation persists or progresses despite ICS therapy.[1,6,7] In addition, antileukotrienes and antihistamines have been suggested as potential therapeutic agents for treatment of NAEB.[1,8] However, to the best of our knowledge, there has been no public report on such trials in English literature.

Cysteinyl leukotrienes (cys-LTs) play important role in the pathogenesis of allergic inflammation, with compelling evidence of upregulation of cys-LTs in both asthma and NAEB.[9–16] Though the anti-inflammatory effects of montelukast (MONT) are generally believed to be milder as compared to ICS in GINA guidelines on asthma,[17] for most studies on add-on MONT in asthma, MONT conferred addictive anti-inflammatory effects to ICS, with better symptom control, improvement of lung function, protection against airway narrowing as compared to double-dose ICS.[11–13] In addition, many *in vivo* and *in vitro* studies support that the proinflammatory pathway of cys-LTs are independent of those suppressed by corticosteroids.[9,10]

Similar to previous studies,[14,15] our previous work also detected elevation of cys-LTs in induced sputum in patients with NAEB,[16] suggesting involvement of cys-LTs in the pathogenesis of NAEB. Accordingly, we hypothesized that MONT as a potent and selective cys-LTs receptor antagonist (LTRA), might confer addictive anti-inflammatory effects to ICS in NAEB, and conducted a 4-week, single-centre, open-label, randomized controlled trial to study the efficacy and tolerability of BUD-MONT combination therapy as compared to double-dose BUD in patients with steroid-naïve NAEB.

Methods

Subjects

Of 764 patients presented with chronic cough (defined as cough lasting over 8 weeks without overt clinicoradiological evidence of lung disease[18]) seen by Drs Cai, Tang, NS Zhong and SQ Zhong at the respiratory specialist clinic of the First Affiliated Hospital of Guangzhou Medical University between May 2010 and February 2011, 65 were diagnosed with steroid-naive NAEB according to the 2006 ACCP guidelines.[1] Following the anatomic diagnostic protocol recommended by the 2006 ACCP cough guidelines,[18] after careful exclusion of active cigarette smoking, exposure to commonly-reported occupational allergens or sensitizers as possible causes of NAEB,[19] co-morbidity with allergic rhinitis (AR) and/or gastroesophageal reflux disease (GERD),[20,21] only 26 patients (40.0%) willing to participate in the study were successfully recruited (Fig. 1). Patients with the following conditions were also excluded: history of taking antileukotrienes, angiotensin converting enzyme inhibitors or bacterial/viral respiratory infections within 14 days prior to enrollment, pregnant or lactating women, known allergy to MONT or BUD, inability to use ICS correctly despite repeated instructions, presence of malignancy undergoing active therapy, life-threatening co-morbidities such as severe heart, lung, liver or kidney diseases. All the participants gave written informed consents. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University.

Subjects were then randomized into the BUD Group (13 patients, BUD 400 μg twice daily, 4 weeks) or BUD-MONT

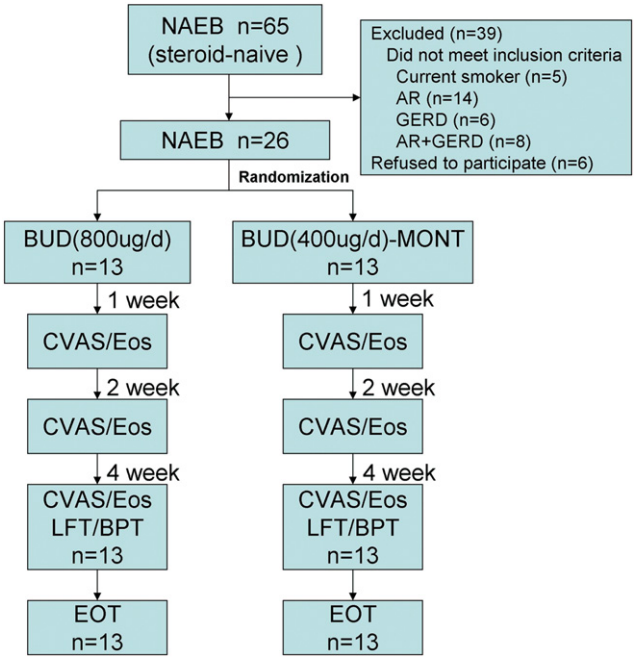

Figure 1 Patient flow. EOT = end of therapy.

Group (13 patients, MONT 10 mg/d plus BUD 200 μg twice daily, 4 weeks) (Fig. 1). Sputum induction and CVAS scoring were conducted at baseline, Week 1, 2 and 4. Spirometry and bronchial provocation test were performed at baseline and Week 4 (end of therapy). Patients were encouraged to record any adverse event and report these events to their treating physicians. Evaluation of adverse events and verification of compliance with treatment (tablet counting and assessment of turbuhaler use) were done at each visit (scheduled at Week 1, 2 and 4). During the study period, systemic corticosteroids, antihistamines, beta 2-agonist, antitussives or protussives (expectorants) and angiotensin converting enzyme inhibitors were prohibited.

Singulair® (Merck & Co., Hangzhou, China) tablets containing 10 mg MONT sodium per tablet and Pulmicort Turbuhaler® (AstraZeneca, Lund, Sweden) with 100 μg BUD power delivered per puff were used in this study.

Our co-primary endpoints were CVAS and Eos at baseline and during treatment, secondary endpoint was adverse events during treatment.

Measurements

Similar to our previous study, spirometry was performed using a dry spirometer (Masterscreen IOS, Jaeger, Würzburg, Germany); airway hyperresponsiveness was determined using histamine challenge (tidal breathing) with PC_{20} histamine >7.8 mg/mL interpreted as negative; atopy was determined by skin prick test for 12 common aeroallergens including house dust mites, cockroaches, animal furs, mold and grass pollens (ALK-Abelló, Hørsholm, Denmark); sputum induction was performed by inhalation of nebulized 4.5% hypertonic saline with 400 nonsquamous cells counted for every sputum specimen.[19] The technician responsible for sputum induction and processing for total and differential cell counts was blinded to the grouping of the subjects. Spirometry and bronchial provocation test with histamine challenge generally preceded sputum induction. For each subject, the tests were repeated in the same sequence and conducted at the same time of the day.[4,19] Cough severity was assessed using CVAS, a 100 mm horizontal visual analogue scale with 0 being no cough and 100 equalling to the worst cough ever.[4,22]

Statistical analysis

Normally distributed data were expressed as mean (SEM), log normally distributed data (Eos) was described as geometric mean (SEM) and non-normally distributed data (cough duration) were described as median. Numeric variables were compared with One-way ANOVA or Mann–Whitney *U* test (cough duration) whereas categorical data was examined with Pearson chi-square test. Pearson's correlation test was used to assess correlation between CVAS and Eos (log transformed). Changes of FEV_1% predicted and FEV_1/FVC at baseline and end of therapy were analyzed using paired Student's *t* test. All hypothesis tests were two-sided, and $p < 0.05$ was defined as significant. SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Demographic, clinical and laboratory characteristics of subjects with NAEB (Fig. 1 and Table 1)

Steroid-naive NAEB accounted for 8.9% of patients presented with chronic cough in this specialist clinic. As demonstrated in Fig. 1, of 65 patients with steroid-naive NAEB, 21.5% had AR as co-morbidity, 9.2% had GERD, and 12.3% had both AR and GERD.

As shown in Table 1, the two groups were comparable in age, gender distribution, cough duration, atopy status, baseline FEV_1% predicted, FEV_1/FVC ratio, Eos (log transformed) and CVAS ($p > 0.05$ for all variables). All subjects tested negative for airway hyperresponsiveness with PC_{20} histamine>7.8 mg/mL.

Changes of Eos during treatment (Fig. 2)

As demonstrated in Fig. 2, for subjects in BUD or BUD-MONT, compared with baseline values (25.37% ± 5.59, 95CI 13.19–37.51 vs 21.08% ± 5.54, 95CI 8.99–33.16), both treatments substantially reduced Eos since Week 1 ($p < 0.0001$ at each treatment course), with reduction of

Table 1 Patients' baseline demographic, clinical and laboratory data.

	BUD ($n = 13$)	BUD-MONT ($n = 13$)	*p*
Age(range), yr	36.2 ± 12.4(22–65)	38.6 ± 12.5(19–55)	0.643
Gender (F:M)	9:4	8:5	0.680
Cough duration, Median(range),mo	8(4–32)	9(5–26)	0.836
Atopy	53.8%	46.2%	0.695
FEV_1% predicted	93.1% ± 4.37	91.3% ± 4.63	0.309
FEV_1/FVC	79.2% ± 3.77	80.6% ± 3.12	0.310
AHR	Negative	Negative	1.00
Eos(range)	3.5%–70.6%	3.2%–65.1%	
GM(SEM)	25.37% ± 5.59	21.08% ± 5.54	0.487
CVAS(range), mm	70.4 ± 8.28(60–85)	73.5 ± 7.94(60–80)	0.288

yr = year, mo = month, AHR = airway hyperresponsiveness, CVAS = cough visual analogue score, Eos = eosinophil differential count in induced sputum, GM = geometric mean.

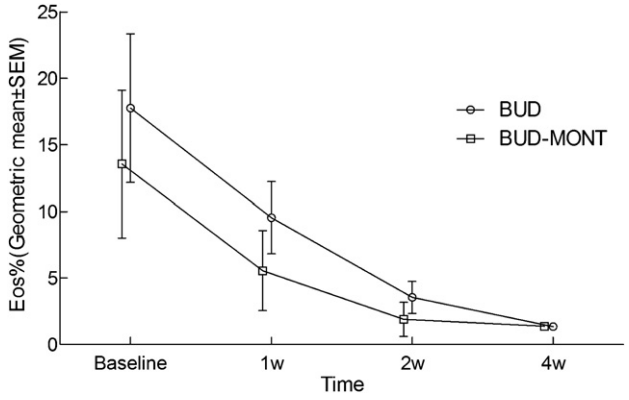

Figure 2 Changes of Eosinophil differential count in induced sputum (Eos) during treatment.

Eos being in parallel with treatment course, and most profound between baseline and Week 1. At end of therapy, Eos in all subjects was reduced below 3% (BUD vs BUD-MONT, 1.48% ± 0.16, 95% CI 1.13—1.84 vs 1.44 ± 0.12, 95%CI 1.19—1.69). There was no significant difference between the two groups for reduction of Eos at each treatment course ($p > 0.05$).

Changes of CVAS during treatment (Fig. 3)

As demonstrated in Fig. 3, for subjects in BUD or BUD-MONT, compared with baseline values (70.4 ± 2.30 mm, 95% CI 65.38—75.40 vs 73.85 ± 2.20 mm, 95% CI 69.04—79.85), both treatments substantially reduced CVAS since Week 1 (mean difference 9.61 mm, 95% CI 3.57—15.67, $p = 0.002$ vs mean difference 14.2 mm, 95% CI 7.60—20.87, $p < 0.0001$), with reduction of CVAS being in parallel with treatment course, and most profound in the last two weeks of treatment. In addition, for both groups, the decrease of CVAS was statistically significant between baseline and 1 week of treatment, 1 week and 2 week of treatment, 2 week and 4 week of treatment ($p < 0.01$) at each time interval. There was no significant difference between the two groups for reduction of CVAS at each treatment course.

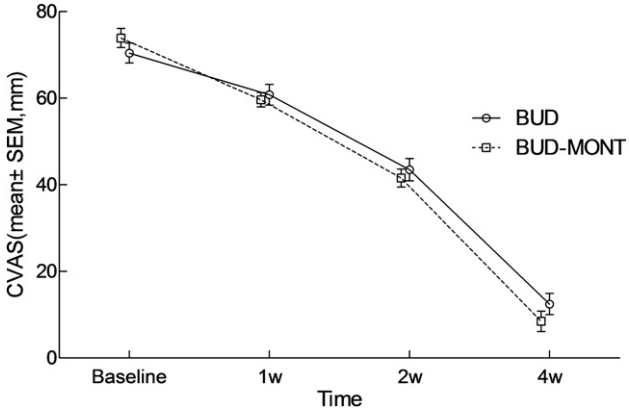

Figure 3 Changes of cough visual analogue scale (CVAS) during treatment.

Association between CVAS and Eos at baseline and during treatment

Similar to the observation by Berry et al,[6] though the reduction of CVAS and Eos was in parallel with the treatment course, there was no significant correlation between CVAS and Eos at baseline and at each time point during treatment when analyzed by Pearson's correlation test.

Spirometric parameters at baseline and end of therapy

For subjects in BUD or BUD-MONT, there was no significant change in FEV_1 % predicted (mean difference −0.42%, 95% CI −0.35—0.87, $p = 0.67$ vs mean difference −0.31%, 95% CI −1.61—0.99, $p = 0.62$) and FEV_1/FVC (mean difference −1.17%,95%CI −0.22—2.36, $p = 0.054$ vs mean difference −1.55%, 95%CI −1.12—4.23, $p = 0.23$) at baseline and end of therapy.

All subjects tested negative for airway hyperresponsiveness with PC_{20} histamine>7.8 mg/mL at end of therapy. All subjects completed the preliminary study. Both regimens were well tolerated without significant adverse events reported during treatment.

Discussion

We describe for the first time that add-on MONT is similar to double-dose BUD (800 μg/d), the generally suggested regimen to treat NAEB, in suppressing eosinophilic airway inflammation and reducing cough severity in patients with steroid-naive NAEB, suggesting a possible adjunctive anti-inflammatory role of LTRAs in NAEB similar to such effects in asthma.

To accurately evaluate the anti-inflammatory effects of both regimens on cough symptom in these subjects presented with chronic cough, stringent eligibility criteria were applied to exclude medical conditions other than NAEB as causes of chronic cough. As a consequence, only 40% patients were successfully recruited, with 50.7% excluded for having co-morbidities that might hinder the interpretation of the impact of inflammation suppression on cough severity. In sharp contrast to the abundance of subjects with asthma,[11—13] this also highlighted the difficulty in recruiting sufficient number of subjects with NAEB in clinical practice.[2,4—7,19,23] This limitation has many ramifications: possible reduction of the statistical power, difficulty in calculating optimal sample size for non-inferiority study, and impairment in sub-division of subjects especially when dose-response to different treatment regimens is the primary outcome measure.

Before we can elaborate on the clinical effects of the two regimens, it is utmost important to clarify a critical point raised by the reviewers: whether 400 μg/d BUD monotherapy is adequate to suppress eosinophilic inflammation and reduce cough in NAEB, as there is an overt defect with the study design: lack of a control group or a run-in period to assess the clinical effects of 400 μg/d BUD. Though we cannot rule out such a possibility, however, the following arguments should be taken into

consideration: firstly, with the different response to ICS, the optimal dose of ICS is not defined in the 2006 ACCP clinical practice guidelines on chronic cough due to NAEB[1]; secondly, later on, as put by the Gonlugurs in their review,[3] 800 μg/d BUD or equivalent dose of fluticasone is generally suggested and widely used to treat NAEB, with suppression of airway eosinophilia and reduction of cough symptom.[2–5] Occasionally (2 in 7 with 800 μg/d beclomethasone; 2 in 32 with 200–400 μg/d BUD), oral corticosteroids are required when low to medium dose ICS failed.[1,6,7] Though dose response to ICS is difficult to establish in NAEB, based upon the above-mentioned clinical data (800 μg/d instead of 400 μg/d is the commonly used dose of BUD for steroid-naive NAEB, and occasionally ICS at such dose could not suppress eosinophilic inflammation and prevent disease progression in NAEB), it is reasonable to assume that 400 μg/d BUD monotherapy can not be adequate to suppress eosinophilic inflammation in all patients with steroid-naive NAEB. Finally, even for patients responding to 400 μg/d BUD, with the optimal dose of ICS undetermined in NAEB, the complementary anti-inflammatory role of LTRAs still could not be denied, as one can argue that what about 200 μg/d BUD plus MONT, and so on.

In general, with difficulty to recruit enough subjects to meet the stringent eligibility criteria, and with BUD at 800 μg/d as the generally accepted regimen for treatment of NAEB,[2–5] for a clinical trial aimed to investigate the non-inferiority of add-on MONT to double-dose ICS, it might be understandable and reasonable for we to select BUD at 800 μg/d as the control group, though the inclusion of another control group using 400 μg/d BUD alone could make our observations more convincing.

Sputum eosinophlia as index of eosinophlic airway inflammation, is one of the defining features of NAEB.[1–8] Consistent with previous findings,[2,4,23] significant reduction of Eos was evident on Week 1 following initiation of ICS treatment in both groups, with sputum eosinophilia being absolutely abrogated on Week 4 (Fig. 2). At different time points during treatment, the reduction of sputum eosinophilia achieved by add-on MONT was similar to that achieved by double-dose BUD. In both groups, the suppression of airway eosinophilia was most apparent following 1 week of treatment, with sustained anti-inflammatory effects throughout the 4-week treatment course.

This complementary anti-inflammatory effect conferred by MONT is similar to the results demonstrated in most studies investigating adjunctive therapy with anti-leukotrienes in asthma.[11–13,17] Since airway eosinophilia and significant elevation of cys-LTs in airway milieu are evident in both NAEB and asthma,[1,9,10,14–16] the suppression of eosinophilic inflammation achieved by MONT might act through similar mechanisms in the two eosinophilic airway diseases.

The successful suppression of eosinophilic airway inflammation by add-on therapy with MONT, may point to novel therapeutic target for NAEB, with potential to avert side effects associated with systemic corticosteroids and to spare the doses of ICS required to maintain control of eosinophilic inflammation and cough symptom. This might be especially meaningful for patients intolerant of ICS, or unresponsive to ICS which necessitated oral corticosteroid therapy.[1,6,7]

In these patients presenting with isolated, irritating and unproductive chronic cough, both regimens substantially decreased CVAS, the subjective measurement of cough severity and response to therapy (Fig. 3). In both groups, the antitussive effects were evident since Week 1, sustained throughout the treatment period, and most apparent in the last two weeks. Add-on MONT was similar to double-dose BUD in suppressing cough at all time points. This reduction of cough severity was consistent with previous findings with ICS in NAEB,[4,5] whereas the authors demonstrated for the first time that add-on therapy with MONT conferred complementary and similar antitussive effects to double-dose ICS.

The antitussive effect of MONT demonstrated in NAEB might be similar to the reduction of cough achieved by LTRAs in cough-variant asthma (CVA),[24–26] as CVA and NAEB share many clinical and immunopathological features with cough as predominant symptom.[27,28] In patients with CVA, LTRAs such as MONT or zafirlukast substantially improved objective and subjective measures of cough severity and suppressed the heightened cough reflex.[24–26] In addition, in patients with CVA,treatment with zafirlukast was shown to suppress chronic cough unresponsive to prolonged ICS therapy,[24] suggesting that similar to its anti-inflammatory effects, the antitussive effect of LTRA may be independent of the corticosteroid pathway.

Brightling et al reported that eosinophilic airway inflammation was causally associated enhanced cough reflex sensitivity in NAEB.[4] In this study the improvement of cough seemed to parallel with the reduction of airway eosinophilia during therapy. However, similar to the findings by Berry et al,[6] no significant correlation was found between CVAS and Eos at baseline and during therapy. This is consistent with the nature of airway inflammation in NAEB, as airway eosinophilia and epithelial infiltration of activated mast cells are two important histological features of NAEB.[1,3,8,27,28] In this case, airway eosinophilia seems to be just one of the many contributing factors causing chronic cough in NAEB.

CVAS, as a valid tool to measure cough severity and monitor clinical efficacy,[22] has been being used in study on NAEB.[4] However, as a subjective measurement, it has inherent limitations to accurately and objectively reflect changes in cough severity and clinical response to antitussive therapy. The dissociation between CVAS and Eos further demonstrated the complex relationship between airway inflammation and the clinical expression of NAEB.

At end of therapy (4 weeks), all the 26 subjects demonstrated significant reduction in airway eosinophilia and cough symptom. There was not any significant adverse reaction reported by the subjects, with both regimens being well tolerated. The good compliance profile might result from the satisfactory therapeutic effects achieved by both regimens as well as be related to the short study period and small sample size. The safety profile of MONT demonstrated in this study is in accordance with those observed in large-sample studies (adverse reactions reported in 14 out of 6158 adult patients[29]) or systemic reviews.[30,31] Careful and repeated instructions on correct use of ICS, the short study period, small sample size, low to

medium-dose BUD used (for example, incidence of oral candidiasis is less than 3% in asthmatics receiving BUD 800 μg/d[32]), health condition of the subjects all might contribute to the absence of significant side effects with ICS in this study.[32]

In addition to the lack of a control group or run-in period to evaluate the clinical effects of 400 μg/d BUD monotherapy in NAEB, there are several other limitations with this preliminary study: Firstly, we acknowledge the limitation associated with the open-label protocol. Possible observer bias in the assessment of cough severity could be prevented with the double-blind design providing placebo to MONT. Secondly, similar to previous studies on NAEB,[2,4–7,14–16,19,23] this study is also limited by its relative small sample size, which might decrease its statistical power, have hindered the sub-division of subjects and the assessment of non-inferiority between the two regimens. Though, at present, this study with 26 subjects is second only to Berry and colleagues' with 32 subjects as for sample size,[2,4–7,14–16,19,23] and it has long been recognized that it is not easy to recruit large number of patients with NAEB in one single institution,[1,8] multi-centre cooperation may provide enough patients.

Conclusion

In this pilot study, we found that add-on MONT could achieve similar anti-inflammatory and antitussive effects to double-dose ICS (800 μg/d BUD) in steroid-naive NAEB, pointing to LTRAs as new therapeutic target in the treatment of NAEB, highlighting the involvement of cys-LTs in the pathogenesis of NAEB. Multi-centre randomized placebo-controlled trial with inclusion of another control group to clarify the clinical effect of 400 μg/d BUD monotherapy is warranted to confirm the adjunctive role of LTRAs in treating NAEB.

Authors' contributions

Dr. Cai conceived the idea, designed the protocol, is the principle investigator of the project and vouches for the integrity of all the contents in the manuscript. Drs Cai, Tan, Zhong NS and Zhong SQ are responsible for patient recruitment and management. Mrs He and Sun are responsible for data collection and processing. Miss Chen is in charge of sputum induction and processing.

Conflict of interest statement

Though Dr. Cai, has received the Merck MISP grant (#37393), similar to all the co-authors, have no other personal conflict of interests to declare.

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